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EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 04/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/749,527

Applicant(s)

KOO ET AL.

Examiner

Angela Bertagna

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-44 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9/10/2004.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: ____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-15 are indefinite, because claim 13 recites the limitation "the target molecule" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Kneipp et al. (US 2002/0150938 A1).

The instant claims are drawn to a method of detecting a nucleotide or nucleoside using surface enhanced raman spectroscopy (SERS).

With regard to claim 1, Kneipp teaches a method comprising:

(a) separating a purine or pyrimidine base from a ribose or deoxyribose moiety of a nucleotide or nucleoside (paragraph 63)

(b) depositing the separated base on a SERS substrate (paragraphs 63 & 48)

(c) detecting the separated base using SERS (paragraphs 63 & 57).

With regard to claim 2, Kneipp teaches detection of a dNTP (claim 20, page 10).

With regard to claim 3, Kneipp teaches fragmenting the DNA or RNA sample with an exonuclease (paragraphs 63-64). This mixture of DNA or RNA and exonuclease is a sequencing mixture.

With regard to claim 4, Kneipp teaches labeling with a Raman label prior to SERS detection (paragraph 42).

With regard to claims 5-7, Kneipp teaches detection of nucleotides comprising the purine bases adenine and guanine (see claim 19, page 10).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 8-12 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1) in view of Liang et al. (Chemical Physics Letters, 1994).

The instant claims are drawn to a method of detecting a nucleotide or nucleoside using surface enhanced coherent anti-Stokes raman spectroscopy (SECARS).

Kneipp teaches the method of claim 1, as discussed above.

With regard to claim 8, Kneipp teaches the use of SERS for detection, but not SECARS.

With regard to claims 9-12, Kneipp teaches detection of pyrimidine bases including thymine, cytidine, and uracil (see claim 19, page 10).

With regard to claim 16, Kneipp teaches a method comprising:

- (a) isolating the target molecule (paragraph 63)
- (b) depositing the target on a SERS substrate (paragraphs 63 & 48)
- (c) detecting the target with SERS (paragraphs 63 & 57).

Kneipp teaches SERS detection rather than SECARS.

With regard to claim 17, Kneipp does not specifically teach isolation of DNA or RNA from biological materials. However, the cited references (US Patent No. 5,674,743) teach isolation from biological samples, thereby demonstrating that Kneipp contemplated sequencing DNA isolated from biological sources.

With regard to claims 19-23, Kneipp teaches detection of dNTPs and also pyrimidine bases including thymine, cytidine and uracil (see claims 19-20, page 10).

Liang reports the experimental observation of SECARS (abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use SECARS to detect nucleotides or nucleotide bases in the SERS-based method of Kneipp. Liang taught that surface enhancement (SECARS) produced a Raman signal significantly enhanced relative to CARS with improved signal-to-noise (abstract). Since the CARS method, which results from excitation with dual lasers, was known to produce a greater signal relative to spontaneous Raman scattering (the source of the SERS signal), the person of ordinary skill would have been motivated to combine surface enhancement with the CARS technique as suggested by Liang in order to improve the sensitivity of the detection method of Kneipp. Since the only required modification to the SERS-based detection would have been incorporation of CARS laser sources, the person of ordinary skill would have expected a reasonable level of success in substituting SECARS for SERS in the method of Kneipp. Therefore, the ordinary practitioner of the SERS detection method of Kneipp, interested in obtaining a more sensitive detection method, would have been motivated to substitute SECARS detection as suggested by Liang, thus resulting in the instantly claimed methods.

6. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (US 2002/0150938 A1) in view of Vo Dinh (Trends in Analytical Chemistry, 1998).

The instant claims are drawn to the method of claim 1, further comprising deposition of the target molecule on silver nanoparticles and contacting the nanoparticle-immobilized targets with an alkali-halide salt, specifically, lithium chloride.

Kneipp teaches the method of claim 1, as discussed above.

With regard to claim 13, Kneipp does not teach the use of silver nanoparticles.

With regard to claims 14-15, Kneipp teaches that lithium is a SERS-active metal (paragraph 48) and further teach contacting the aggregate-immobilized nucleotides with an alkali metal halide salt, specifically a silver halide solution (paragraph 53).

Vo-Dinh teaches that silver nanoparticles are particularly useful for SERS applications requiring reproducible results (page 565, column 2). Vo-Dinh also teaches “silver-coated nanospheres were found to be among the most strongly enhancing substrates investigated, with enhancement factors comparable to or greater than those found in electrochemically roughened surfaces” (page 567).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to deposit the separated nucleotides prepared by the method of Kneipp on silver nanoparticles prior to detection using SERS. Vo-Dinh particularly pointed out the advantages of using silver nanoparticles for SERS detection, namely increased reproducibility and signal enhancement (pages 565 and 567, respectively). These teachings of Vo-Dinh would have strongly motivated the ordinary practitioner of the SERS method of Kneipp to deposit separated nucleotides onto silver nanoparticles rather than the metal aggregates taught by Kneipp in order to minimize experimental variability and enhance the Raman signal. Since Kneipp taught deposition of the separated nucleotide on metal aggregates of nanometer-micrometer scale (see

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abstract), the ordinary practitioner would have expected a reasonable level of success in substituting silver nanoparticles. Furthermore, since Kneipp taught the use of a silver halide solution to generate silver aggregate formation and surface-enhanced Raman excitation (paragraph 53), and further taught that lithium was also a SERS-active surface (paragraph 43), the person of ordinary skill would have been motivated to utilize any desired SERS-active substrate and alkali-metal halide solution (such as lithium chloride). Therefore, the person of ordinary skill, interested in improving reproducibility and enhancing the Raman signal in the SERS detection method of Kneipp, would have been motivated to deposit the target onto silver nanoparticles, as suggested by Vo-Dinh, thus resulting in the instantly claimed method.

7. Claims 24-28 and 30-37 and 39-40, and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (US Patent No. 6,255,083 B1) in view of Kneipp et al. (US 2002/0150938 A1) and further in view of Vo-Dinh (US Patent No. 5,306,403).

The instant claims are drawn to a method of sequencing a nucleic acid comprising primer extension of an immobilized primer or template and detection of incorporated nucleotides using SERS.

Williams teaches a fluorescence-based single molecule sequencing method utilizing a microflow chamber to continuously flow doubly labeled NTPs past an immobilized target undergoing primer extension.

With regard to claims 24 & 34, the method of Williams comprises (column 2, lines 15-36):

(a) immobilization of target nucleic acid on a solid support

(b) primer extension of the immobilized target using at least one distinguishably labeled dNTP that is detectable upon incorporation into the primer

(c) detecting the signal arising from the incorporated nucleotide.

With regard to claims 24 & 34, Williams teaches fluorescence detection rather than SERS detection.

With regard to claims 25-26, Williams does not teach that the concentrations of the first dNTP and the target are approximately the same or that the target concentration is about one half that of the dNTP, but rather that the template is more concentrated than the nucleotide (see Example 5, column 18, lines 55-59).

With regard to claims 27, 30, and 35-36, the method of Williams is performed in a micro-flow chamber with constant detection (see for example, column 4, lines 1-17 and column 11, line 63 – column 12, line 9). Therefore, additional first nucleotide is added after detection of the first nucleotide, and also the method is performed using different nucleotides. Also, the continuous flow method of Williams provides washing before detecting subsequent NTP incorporation.

With regard to claims 32-33, 39-40, and 43-44, Williams teaches the use of NTPs doubly labeled with a fluorescent dye coupled to the γ -phosphate and a quencher coupled to the nucleobase (column 5, lines 30-54). These NTPs serve as internal controls for the reaction, since a detectable fluorescence signal is only generated when the fluorescent dye is released upon incorporation into the growing primer. Furthermore, since the method of Williams comprises constant detection of doubly labeled NTPs flowing past the immobilized target, the method inherently determines the number and order of incorporated NTPs as well as any pre-incorporation background signal.

With regard to claim 37, Williams teaches acquiring a series of images for 20 minutes (column 18, lines 6-7), thereby implying that the incorporation step is within the claimed range of about 1 second to 10 minutes.

Kneipp teaches a SERS-based sequencing method, as discussed above.

With regard to claims 24 and 34, Kneipp teaches a method comprising:

- (a) separating a purine or pyrimidine base from a ribose or deoxyribose moiety of a nucleotide or nucleoside (paragraph 63)
- (b) depositing the separated base on a SERS substrate (paragraphs 63 & 48)
- (c) detecting the separated base using SERS (paragraphs 63 & 57).

Kneipp does not teach primer extension-based sequencing.

With regard to claim 28, Kneipp teaches sequencing of DNA or RNA by cleaving a base from a nucleotide and detecting the base using SERS (paragraphs 63-64).

With regard to claim 31, Kneipp teaches labeling with a Raman label prior to SERS detection (paragraph 42).

Vo-Dinh teaches a method of DNA sequencing using SERS (see abstract) and particularly points out that fluorescence-based sequencing methods may be misleading since they rely upon signals from labels that display broad, structureless and overlapping spectra (column 2, line 67 – column 3, line 9).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute SERS detection for fluorescence detection in the primer extension-based sequencing method taught by Williams. Kneipp taught that SERS detection was a highly sensitive method of detecting nucleotides and bases, and was particularly useful for sequencing

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applications (see abstract, for example). Vo-Dinh further taught that SERS detection was preferable to fluorescence detection in DNA sequencing applications, because fluorescence-based methods suffer from inaccuracies due to the fact that many commonly used fluorescent dyes display broad, structureless and overlapping spectra. These teachings of Kneipp and Vo-Dinh would have motivated the person of ordinary skill to incorporate SERS detection into the fluorescence-based method of Williams.

Regarding claims 25-26, Williams, Kneipp and Vo-Dinh did not specifically teach using concentrations of the first dNTP and the target are approximately the same or target concentrations that are about one half that of the dNTP. The critical factor in performing the sequencing method resulting from the combined teachings of Williams, Kneipp, and Vo-Dinh is the ability to detect separated and/or newly incorporated nucleotides. Although Kneipp, Williams and Vo-Dinh do not explicitly state that concentrations of the first dNTP and the target are approximately the same or target concentrations that are about one half that of the dNTP, the ordinary practitioner would have recognized that the target and NTP concentrations are not critical provided that the functional limitations (ability to reliably detect separated and/or newly incorporated nucleotides) are satisfied and would have designed optimal target and nucleotide concentrations as taught by Kneipp, Williams, and Vo-Dinh. As noted In re Aller, 105 USPQ 233 at 235:

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

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Routine optimization is not inventive and no evidence has been provided to suggest that the use of the particular target and NTP concentrations was anything other than routine or that the results were unexpected as compared to the closest prior art.

8. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (US Patent No. 6,255,083 B1) in view of Kneipp et al. (US 2002/0150938 A1) and further in view of Vo-Dinh (US Patent No. 5,306,403) and further in view of Liang et al. (Chemical Physics Letters, 1994).

Claim 29 is drawn to the use of SECARS in the method of claim 24.

The combined teachings of Williams, Kneipp, and Vo-Dinh result in the instant claim 24, as discussed above.

None of the above references (Williams, Kneipp, and Vo-Dinh) teach the use of SECARS.

Liang reports the experimental observation of SECARS (abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use SECARS to detect nucleotides or nucleotide bases in the combined method resulting from the teachings of Williams, Kneipp, and Vo-Dinh. Liang taught that surface enhancement (SECARS) produced a Raman signal vastly enhanced relative to CARS with improved signal-to-noise (abstract). Since the CARS method, which results from excitation with dual lasers, was known to produce a greater signal relative to spontaneous Raman scattering (the source of the SERS signal), the person of ordinary skill would have been motivated to combine surface enhancement with the CARS technique as suggested by Liang in order to improve the

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sensitivity of the SERS-based detection method. Since the only required modification to the SERS-based detection would have been incorporation of CARS laser sources, the person of ordinary skill would have expected a reasonable level of success in substituting SECARS for SERS. Therefore, the ordinary practitioner of the SERS detection method resulting from the combined teachings of Williams, Kneipp, and Vo-Dinh, interested in obtaining a more sensitive detection method, would have been motivated to substitute SECARS detection as suggested by Liang, thus resulting in the instantly claimed methods.

9. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (US Patent No. 6,255,083 B1) in view of Kneipp et al. (US 2002/0150938 A1) and further in view of Vo-Dinh (US Patent No. 5,306,403) and further in view of Quake (US Patent No. 6,002,471).

Claim 38 is drawn to the method of claim 34, wherein the reaction chamber is less than 100 nm in at least one dimension.

The combined teachings of Williams, Kneipp, and Vo-Dinh result in the method of claim 34, as discussed above.

Williams teaches the use of a microscale fluidics device, but not a nanoscale device.

Quake teaches a high resolution scanning Raman microscope capable of nanometer level sequencing of DNA based on Raman signals (see abstract and column 2, lines 63-65).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a nanoscale detection device as taught by Quake in the combined method of Williams, Kneipp, and Vo-Dinh in order to decrease sample requirements and improve the resolution of the method. Quake taught that SERS resolution was increased and sample

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requirements decreased relative to the prior art of Kneipp, for example (see column 1, lines 38-59 and column 2, lines 6-21). Since the device taught by Quake was specifically designed for Raman-based DNA sequencing applications, the ordinary user would have been motivated to apply the teachings of Quake, thereby resulting in a reaction chamber having a reduced size (less than 100 nm in at least one dimension, for example), thus resulting in the instantly claimed methods.

10. Claims 24-26, 28, 30-35, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xue et al. (US Patent No. 6,972,174 B2) in view of Kneipp et al. (US 2002/0150938 A1) and further in view of Vo-Dinh (US Patent No. 5,306,403).

The instant claims are drawn to a method of sequencing a nucleic acid comprising primer extension of an immobilized primer or template and detection of incorporated nucleotides using SERS.

Xue teaches a single nucleotide polymorphism (SNP) genotyping method comprising primer extension on array of immobilized primers using different mixtures of nucleotides and identification of the SNP based on the length of the extension product.

With regard to claims 24 & 34, the method of Xeu comprises (column 3, lines 6-36):

(a) immobilization of a primer on a solid support (column 3, lines 10-14)

(b) primer extension of the immobilized target using at least one distinguishably labeled NTP that is detectable upon incorporation into the primer (column 3, lines 15-23)

(c) detecting the signal arising from the incorporated nucleotide and determining the length of the primer extension product to determine the sequence at an unknown position (column 3, lines 15-35).

With regard to claims 24 & 34, Xue teaches fluorescence detection rather than SERS detection.

With regard to claims 25-26, Xue does not teach that the concentrations of the first dNTP and the target are approximately the same or that the target concentration is about one half that of the dNTP.

With regard to claim 30 and 35, Xue teaches repeating steps (a) – (c) above with different nucleotides (see Figure 2 where the same primer is interrogated with multiple different reaction mixtures and also Example 3, column 16, lines 44-66).

With regard to claims 32-33 and 43-44, Xue teach detection of an internal control (see, for example, Figure 2 where a “control mix” is used for primer extension).

With regard to claims 41-42, Xue teaches using dATP and dGTP as the first and second nucleotides with both the target strand (see Figure 8, where dATP and ddGTP are used as the first and second nucleotides; see also Example 3, where a target sequence is amplified using PCR and then one strand is chosen to hybridize with the immobilized primer).

Kneipp teaches a SERS-based sequencing method, as discussed above.

With regard to claims 24 and 34, Kneipp teaches a method comprising:

- (a) separating a purine or pyrimidine base from a ribose or deoxyribose moiety of a nucleotide or nucleoside (paragraph 63)
- (b) depositing the separated base on a SERS substrate (paragraphs 63 & 48)
- (c) detecting the separated base using SERS (paragraphs 63 & 57).

Kneipp does not teach primer extension-based sequencing.

With regard to claim 28, Kneipp teaches sequencing of DNA or RNA by cleaving a base from a nucleotide and detecting the base using SERS (paragraphs 63-64).

With regard to claim 31, Kneipp teaches labeling with a Raman label prior to SERS detection (paragraph 42).

Vo-Dinh teaches a method of DNA sequencing using SERS (see abstract) and particularly points out that fluorescence-based sequencing methods may be misleading since they rely upon signals from labels that display broad, structureless and overlapping spectra (column 2, line 67 – column 3, line 9).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute SERS detection for fluorescence detection in the primer extension-based sequencing method taught by Xue. Kneipp taught that SERS detection was a highly sensitive method of detecting nucleotides and bases. Vo-Dinh further taught that SERS detection was preferable to fluorescence detection because fluorescence-based methods suffer from inaccuracies due to the fact that many commonly used fluorescent dyes display broad, structureless and overlapping spectra. These teachings of Kneipp and Vo-Dinh would have motivated the person of ordinary skill to incorporate SERS detection into the fluorescence-based sequencing method of Xue. Furthermore, with regard to claim 42, although Xue taught hybridization of only one of two complementary strands to an immobilized primer followed by extension and SNP identification, the person of ordinary skill would have recognized that in addition to the control extension reaction shown in Figure 2, the complementary sequence would also provide a useful additional control for the extension reaction.

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Regarding claims 25-26, Xue, Kneipp and Vo-Dinh did not specifically teach using concentrations of the first dNTP and the target are approximately the same or target concentrations that are about one half that of the dNTP. The critical factor in performing the sequencing method resulting from the combined teachings of Xue, Kneipp and Vo-Dinh is the ability to detect separated and/or newly incorporated nucleotides. Although Kneipp, Xue and Vo-Dinh do not explicitly state that concentrations of the first dNTP and the target are approximately the same or target concentrations that are about one half that of the dNTP, the ordinary practitioner would have recognized that the target and NTP concentrations are not critical provided that the functional limitations (ability to reliably detect separated and/or newly incorporated nucleotides) are satisfied and would have designed optimal target and nucleotide concentrations as taught by Kneipp, Xue, and Vo-Dinh. As noted *In re Aller*, 105 USPQ 233 at 235:

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not inventive and no evidence has been provided to suggest that the use of the particular target and NTP concentrations was anything other than routine or that the results were unexpected as compared to the closest prior art.

10. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xue et al. (US Patent No. 6,972,174 B2) in view of Kneipp et al. (US 2002/0150938 A1) and further in view of Vo-Dinh (US Patent No. 5,306,403) and further in view of Liang et al. (Chemical Physics Letters, 1994).

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Claim 29 is drawn to the use of SECARS in the method of claim 24.

The combined teachings of Xue, Kneipp, and Vo-Dinh result in the instant claim 24, as discussed above.

None of the above references (Xue, Kneipp, and Vo-Dinh) teach the use of SECARS.

Liang reports the experimental observation of SECARS (abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use SECARS to detect nucleotides or nucleotide bases in the combined method resulting from the teachings of Xue, Kneipp, and Vo-Dinh. Liang taught that surface enhancement (SECARS) produced a Raman signal vastly enhanced relative to CARS with improved signal-to-noise (abstract). Since the CARS method, which results from excitation with dual lasers, was known to produce a greater signal relative to spontaneous Raman scattering (the source of the SERS signal), the person of ordinary skill would have been motivated to combine surface enhancement with the CARS technique as suggested by Liang in order to improve the sensitivity of the SERS-based detection method. Since the only required modification to the SERS-based detection would have been incorporation of CARS laser sources, the person of ordinary skill would have expected a reasonable level of success in substituting SECARS for SERS. Therefore, the ordinary practitioner of the SERS detection method resulting from the combined teachings of Xue, Kneipp, and Vo-Dinh, interested in obtaining a more sensitive detection method, would have been motivated to substitute SECARS detection as suggested by Liang, thus resulting in the instantly claimed methods.

Double Patenting

11. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

12. Claims 1-44 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-44 of copending Application No. 11/020,776. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-2, 4, and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, 9, and 12 of copending Application No. 10/108,128. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of claims 1, 6 and 12 of Application No. 10/108,128 recite specific embodiments of the generic methods of the instant claim 1, and therefore, anticipate this claim. The limitations of the instant claim 2 are recited in claims 1 and 12 of 10/108,128. The limitations of the instant claim 4 are recited in claim 12 of 10/108,128. The limitations of the instant claim 13 are recited in claims 1, 9 and 12 of 10/108,128.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-2, 4 and 13 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-7, and 17-18 of copending Application No. 10/660,902. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 7 of 10/660,902 recite a specific embodiment of the generic method of claim 1, and therefore, anticipate this claim. The limitations of the instant claim 2 are recited in claims 1, 6-7 and 17-18 of 10/660,902. The limitations of the instant claim 4 are recited in claims 6 and 17 of 10/660,902. The limitations of the instant claim 13 are recited in claim 7 of 10/660,902.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-2, and 4 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 20-21, and 24 of copending Application No. 11/255,386. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 17, 20-21 and 24 of 11/255,386 recite a specific embodiment of the generic method of the instant claim 1, and therefore, anticipate this claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-2, 4, 5-6, 9-10, and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5-10, and 12 of copending Application No. 11/270,211. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 9-10 and 12 of 11/270,211 recite a specific embodiment of the generic method of the instant claim 1. The limitations of the instant claim 2 are recited in claims 1 and 3 of 11/270,211. The limitations of the instant claim 4 are recited in claim 5 of 11/270,211. The limitations of the instant generic claims 5-6, 9-10 and 12 are anticipated by the specific embodiments disclosed in claims 6-8 of 11/270.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are currently allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Angela Bertagna
Art Unit 1637

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KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

4/13/06